

Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19

Rodolfo Pedro Rothlin¹  | Héctor Miguel Vetulli² | Mariano Duarte^{3,4} | Facundo Germán Pelorosso⁵

¹Sociedad Argentina de Farmacología Clínica, Asociación Médica Argentina, Buenos Aires, Argentina

²Servicio de Electrofisiología Cardíaca, Arritmias y Marcapasos, Sanatorio Otamendi y Mirolli, Buenos Aires, Argentina

³Hospital de Clínicas "José de San Martín", Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

⁴Segunda Cátedra de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

⁵Department of Pathology, Hospital de Alta Complejidad El Calafate SAMIC, Santa Cruz, Argentina

Correspondence

Rodolfo Pedro Rothlin, Sociedad Argentina de Farmacología Clínica, Asociación Médica de Argentina, Buenos Aires, Argentina.
Email: safc@ama-med.org.ar

Abstract

In late 2019, a new coronavirus emerged in Wuhan Province, China, causing lung complications similar to those produced by the SARS coronavirus in the 2002–2003 epidemic. This new disease was named COVID-19 and the causative virus SARS-CoV-2. The SARS-CoV-2 virus enters the airway and binds, by means of the S protein on its surface to the membrane protein ACE2 in type 2 alveolar cells. The S protein-ACE2 complex is internalized by endocytosis leading to a partial decrease or total loss of the enzymatic function ACE2 in the alveolar cells and in turn increasing the tissue concentration of pro-inflammatory angiotensin II by decreasing its degradation and reducing the concentration of its physiological antagonist angiotensin 1–7. High levels of angiotensin II on the lung interstitium can promote apoptosis initiating an inflammatory process with release of proinflammatory cytokines, establishing a self-powered cascade, leading eventually to ARDS. Recently, Gurwitz proposed the tentative use of agents such as losartan and telmisartan as alternative options for treating COVID-19 patients prior to development of ARDS. In this commentary article, the authors make the case for the election of telmisartan as such alternative on the basis of its pharmacokinetic and pharmacodynamic properties and present an open-label randomized phase II clinical trial for the evaluation of telmisartan in COVID-19 patients (NCT04355936).

KEYWORDS

ACE2, angiotensin II, ARDS, clinical trial, COVID-19, SARS-CoV-2, telmisartan

In late 2019, a new coronavirus emerged in Wuhan Province, China, causing lung complications similar to those produced by the SARS coronavirus (SARS-CoV) in the 2002–2003 epidemic. This new disease was named COVID-19 and the causative virus SARS-CoV-2 (Chen, Liu, & Guo, 2020; Li et al., 2020).

Given that vaccines against COVID-19 are still in development and an effective treatment against this new coronavirus is lacking, various pharmacological agents are being tested in clinical trials designed by institutions such as the WHO or scientific entities in different countries (Lu, Chen, & Chang, 2020a).

Taking into account the characteristics of the mode of entry of this coronavirus to human cells through binding with Angiotensin

Converting Enzyme 2 (ACE2) and extensive scientific and clinical evidence information on the Renin Angiotensin System, the hypothesis of the involvement of this system in the pathophysiology of COVID-19 was born (Gurwitz, 2020; Vaduganathan et al., 2020).

The SARS-CoV-2 virus enters the airway and binds, by means of the S (Spike) protein on its surface (after whose image the term coronavirus is coined), to the membrane protein ACE2 in type 2 alveolar cells (Lu et al., 2020b; Wan, Shang, Graham, Baric, & Li, 2020). The S protein-ACE2 complex is internalized by endocytosis and facilitates the entry of each virion into the cytoplasm. For each intracellular entry, the function of one ACE2 molecule is lost leading to a partial decrease or total loss of the enzymatic function

ACE2 in the alveolar cells of the lung directly related to the viral load of the air inoculum.

ACE2 catalyzes the transformation of angiotensin II into angiotensin 1–7. Angiotensin II acting on AT1 receptors causes vasoconstriction, apoptosis, proinflammatory effects, and fibrosis. Angiotensin 1–7 acting on Mas receptors causes opposite effects: vasodilation and anti-inflammatory. Partial decrease or total loss of ACE2 function in alveolar cells results in a deviation of the homeostatic balance of the Renin Angiotensin System in favor of the angiotensin II-AT1 receptor axis (Paz Ocaranza et al., 2020; Tikellis, Bernardi, & Burns, 2011). Indeed, it increases the tissue concentration of angiotensin II by decreasing its degradation and reduces the concentration of its physiological antagonist angiotensin 1–7 (Liu et al., 2020).

The clinical manifestations of COVID-19 disease will depend fundamentally on the degree of alteration of the homeostatic balance of the Renin Angiotensin System in the lung and at the systemic level (mainly at the heart).

Increasing the effects of angiotensin II on the lung interstitium can promote apoptosis, which, in turn, initiates an inflammatory process with release of proinflammatory cytokines, establishing a self-powered cascade (Cardoso et al., 2018). In certain patients, this process reaches such clinical relevance that requires external oxygen supply and in severe cases an Acute Respiratory Distress Syndrome (ARDS) ensues (this correlates with an acute release -storm- of cytokines) (Ware & Matthay, 2000).

Based on the aetiopathogenic hypothesis described, there are various pharmacotherapeutic proposals to be evaluated through clinical trials: Recombinant ACE2 therapy, administration of agents aimed at increasing ACE2 levels (e.g., estradiol), and administration of drugs that decrease the elevated activity of angiotensin II including renin release inhibitors, classic ACE inhibitors (ACEI), or Angiotensin Receptor 1 Blockers (ARBs).

Most patients who develop COVID-19 disease initially have fever, indicative of an inflammatory process with systemic release of pyrogenic cytokines. According to the hypothesis described, this inflammation is induced by the inhibition of ACE2 and the imbalance of the renin angiotensin system in the pulmonary interstitium in favor of the angiotensin II-AT1 receptor axis. Faced with the onset of the inflammatory process, a rapidly effective treatment is necessary to antagonize the cascading and self-sustaining phenomenon described. Of the different types of drugs mentioned above, we consider that the most rapidly effective may be ARBs.

Recently, Gurwitz (2020) proposed the tentative use of agents such as losartan and telmisartan as alternative options for treating COVID-19 patients prior to development of ARDS. Interestingly, during the revision of this manuscript, Zhang et al. (2020) found that among patients with hypertension hospitalized with COVID-19, inpatient treatment with ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB nonusers.

ARBs are widely used to treat hypertension and there is an abundant clinical experience with its use, all representatives of this group being characterized by their excellent tolerance. Furthermore, its

adverse effects profile has been described as "placebo like" (Schumacher & Mancina, 2008; Sharpe, Jarvis, & Goa, 2001).

The most suitable ARB to antagonize the proinflammatory effects of angiotensin II in a patient with a recent positive COVID-19 test should be the compound with the best pharmacological properties for this indication. From the comparative analysis of the available ARBs, telmisartan gathers properties that make it the best pharmacological tool to evaluate the hypothesis under discussion in a clinical trial.

Liposolubility is relevant for absorption after oral administration and for tissue penetration. Telmisartan stands out among all the representatives of the ARBs for being markedly more lipophilic, expressed both in partition coefficients (octanol/neutral pH buffer), distribution coefficients and distribution volumes (Vd). Telmisartan has a Vd of approximately 500 L, irbesartan 93 L, and both valsartan and olmesartan, candesartan and losartan, approximately 17 L.

The affinity of ARBs for the AT1 receptor has been measured by multiple studies, mainly using radioligand binding studies. All AT1 receptor blockers are characterized by having similar affinity values (pKi or pIC50, between 2 and 19 nM), with losartan and its active metabolite EXP3174 being the lowest and irbesartan, candesartan, and telmisartan the highest (Kakuta, Sudoh, Sasamata, & Yamagishi, 2005).

Using isolated organ technique on blood vessels from different tissues and from different animals, these AT1 antagonists have a blocking power (pA2) against angiotensin II in the nM range (losartan, 8.15; irbesartan, 8.52; valsartan, 9.26; telmisartan 9.48; candesartan, 10.08). Telmisartan has a 10-fold higher blocking potency than losartan (Kakuta et al., 2005).

Functional as well as biochemical studies determining the dissociation rates of the ARBs have shown that these drugs have a slow dissociation rate that gives them characteristics of pseudo-irreversible blocking agents. In the only comparative study using cloned human AT1 receptors, the half-lives of receptor dissociation were: telmisartan, 213 min; olmesartan, 166 min; candesartan, 133 min; valsartan, 70 min; losartan, 67 min (Kakuta et al., 2005). Telmisartan is the AT1 blocker that dissociates more slowly from the receptor. This property may be clinically relevant as it maintains a longer lasting blockade difficult to reverse by the endogenous agonist angiotensin II.

Furthermore, telmisartan causes downregulation of AT1 receptor at the mRNA and protein level apparently due to its action as a partial agonist of PPAR-gamma (Peroxisome Proliferator-Activated Receptor gamma). This action can contribute to the effects of telmisartan by producing a decrease in the number of AT1 receptors (Imayama et al., 2006).

In summary, telmisartan, which is well absorbed after oral administration, is the ARB with the longest plasma half-life (24 hr), it reaches the highest tissue concentrations due to its high lipid solubility and high volume of distribution (500 L), and dissociates more slowly after binding to the AT1 receptor, causing an apparently irreversible block (Kakuta et al., 2005; Michel, Foster, Brunner, & Liu, 2013).

In accordance with these data, a randomized open-label controlled trial has begun enrolment in Hospital de Clínicas "José de San Martín" (School of Medicine, University of Buenos Aires, Argentina).

The proposed intervention in the clinical trial setting will be Telmisartan (Bertel[®], Laboratorio Elea Phoenix, Buenos Aires, Argentina), 80 mg twice daily, oral administration, beginning upon positive PCR test for COVID-19 versus standard care (NCT04355936).

Clinical studies to evaluate the safety of Telmisartan in healthy individuals or in hypertensive patients with daily doses of up to 160 mg found no difference between those treated with telmisartan and the placebo group in frequency and intensity of adverse effects (Schumacher & Mancía, 2008; Sharpe et al., 2001; Stangier, Su, & Roth, 2000).

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Rodolfo Pedro Rothlin  <https://orcid.org/0000-0003-4731-6099>

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